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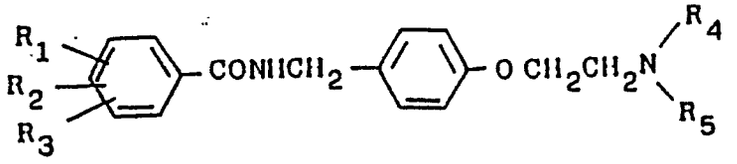
(54) Amide compounds, process for preparing the same, and composition for activating gastric motor function containing the same.

(57) Amide-compounds represented by the formula (I):



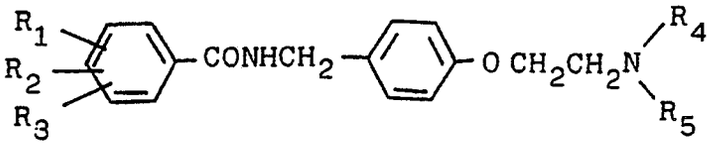
(I)

wherein R_1 represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino which can be substituted by lower alkyl, nitro, cyano, sulfamoyl which can be substituted by lower alkyl, R_2 represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino, nitro, wherein R_1 and R_2 can be combined to form methylenedioxy, R_3 means hydrogen, lower alkyl, halogen, or amino, R_4 and R_5 may be the same or different and each represents lower alkyl or wherein R_4 and R_5 may be combined together with nitrogen to form 1-pyrrolidinyl or piperidino, and pharmacologically-acceptable acid-addition salts thereof, which exhibit excellent effects in the activation of gastric motor function, a process for preparation pharmaceutical compositons thereof, as well as a method for the treatment of a subject suffering from an ailment associated with inadequate gastric motor function by administrating such a compound to the said subject, are all disclosed.

AMIDE COMPOUNDS, PROCESS FOR PREPARING THE SAME, AND COMPOSITION FOR ACTIVATING GASTRIC MOTOR FUNCTION CONTAINING THE SAME

1. Field of the Invention

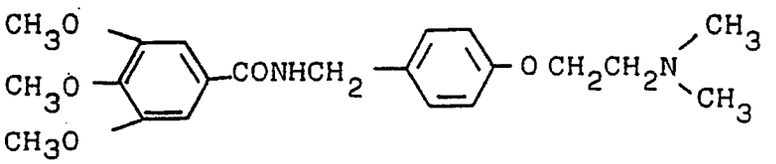
The present invention relates to novel amide compounds represented by the following general formula (I) as well as acid addition salts thereof, process for preparing the same, and a composition for activating gastric motor function containing the same as active ingredient which can be used in the treatment of related ailments.



(I)

2. Description of the Prior Art

It is already known that N-[4-[2-(dimethylamino)ethoxy]benzyl] -3,4,5-trimethoxybenzamide [general name, TRIMETHOBENZAMIDE, The United States Pharmacopeia XXI, 1094 (1985)] represented by formula (II),

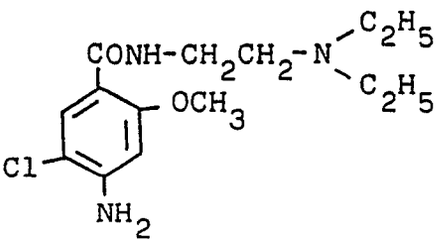


(II)

can be used only as an antiemetic drugs and is not used for activating gastric motor function.

Non-ulcer dyspepsia such as gastric discomfort and abdominal distension results in part from a decrease of gastric motor function. Therefore, it is necessary to administer a drug which has the action on activating gastric motor function, so that such symptons can also be alleviated.

So far, as a medicament which has the action on activating gastric motor function, 4-Amino-5-chloro-N-[(2-diethylamino)ethyl]-2-methoxybenzamide (general name, Metoclopramide, The Merck Index 10th Edition, 6019) represented by formula (III) is known.



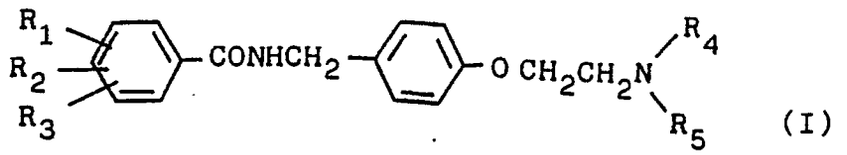
(III)

But this medicament has also the antiemetic effect. Medicaments such as this one are not satisfactory for practical use because of in sufficient efficacy and having the serious side effects.

Accordingly, there has been a need for a new and useful medicament for the activation of the gastric motor function.

3. Summary of the invention

It has been found surprisingly, that the amide compounds represented by the formula (I):



(I)

wherein R_1 represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino which can be substituted by lower alkyl, nitro, cyano, sulfamoyl which can be substituted by lower alkyl, R_2 represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino, nitro, wherein R_1 and R_2 can be combined to form methylenedioxy,R_3 means hydrogen, lower alkyl, halogen, or amino, R_4 and R_5 may be the same or different and each represents lower alkyl or wherein R_4 and R_5 may be combined together with nitrogen to form 1-pyrrolidinyl or piperidino, and pharmacologically-acceptable acid-addition salts thereof, exhibit excellent effects in the activation of gastric motor function.

Further, according to the present invention, there are provided also a process for preparation of the novel amide compounds represented by the general formula (I), pharmaceutical compositions useful to activate gastric motor function comprising one or more compounds as represented by the formula (I) in an amount effective for such purpose, as well as a method for the treatment of a subject suffering from an ailment associated with inadequate gastric motor function by administrating such a compound to the said subject.

DETAILED DESCRIPTION OF THE INVENTION

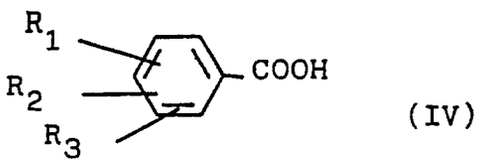
By the term "lower" in formula(I) is meant a straight or branched carbon chain having 1-4 carbon atoms, inductively. Therefore the lower alkyl moiety of the lower alkyl group encompassed by R_1, R_2, R_3, R_4 and R_5 is representatively methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, etc. The lower alkoxy moiety of the lower alkoxy group is representatively methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, etc. As halogen represented by R_1, R_2 and R_3 can be used: fluorine, chlorine and bromine, etc. Examples of amine, which may be substituted by lower alkyl are amino, methylamino, dimethylamino, and diethylamino, etc. and examples of sulfamoyl group, which may be substituted by lower alkyl are sulfamoyl, methylaminosulfonyl and dimethylaminosulfonyl, etc.

The compounds represented by the formula (I) can be converted to their pharmacologically-acceptable acid-addition salts in the usual manner and the free base can be liberated from the resulting salts if desired.

Pharmacologically-acceptable acid-addition salts of the amide compounds represented by the formula (I) include, for example, mineral salts such as hydrochloride, hydrobromide, nitrate, sulfate, phosphate, and the like, or organic acid salts such as acetate, maleate, fumarate, citrate, oxalate, lactate, malate, tartarate, and the like.

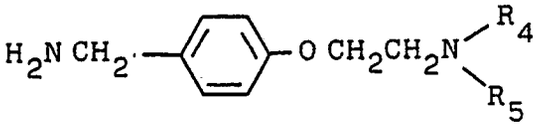
The novel amide-compounds represented by the general formula (I) can be prepared as follows:

A functional derivative such as the chloride or other halide, the anhydride or a mixed anhydride, of a carboxylic acid represented by the formula (IV)



(IV)

wherein R_1, R_2 and R_3 each has the same meaning as described above, is reacted with an amino-compound represented by the formula (V)



(V)

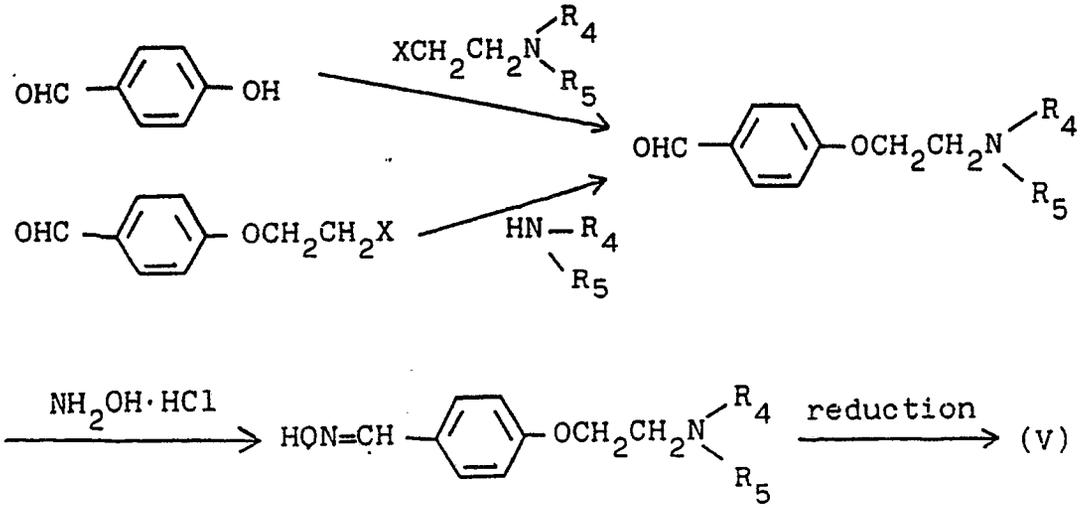
wherein R_4 and R_5 each has the same meaning as described above, in the presence or absence of a base and in the presence of an inert organic solvent.

Bases which can be used in this method are, for example, pyridine, picoline, lutidine, collidine, N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, triethylamine, potassium carbonate, sodium carbonate, or the like.

The solvent used in this reaction can be any kind of solvent which does not inhibit the reaction. Examples of the inert organic solvent which may be used are ether, benzene, toluene, ethyl acetate, tetrahydrofuran, dioxane, chloroform, methylenechloride, dimethylsulfoxide,and N,N-dimethylformamide.

The reaction is generally carried out at a temperature within the range of 0 °C to the reflux temperature of the reaction solvent employed.

The starting materials represented by the above formula (V), most of which are novel compounds, can be prepared by a process shown in the following scheme:



wherein R_4 and R_5 each has the same meaning as described above and X represents a halogen.

The most important compounds of this invention are for example as follows:
N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide, N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide hydrochloride, 3,4-Methylenedioxy-N-[4-[2-(1-pyrrolidinyl) ethoxy]benzyl] benzamide, 3,4-Dimethoxy-N-[4-[2-(1-pyrrolidinyl) ethoxy]benzyl]benzamide, N-[4-[2-(dimethylamino)ethoxy]benzyl]-4-ethoxy-3-methoxybenzamide,
N-[4-[2-(dimethylamino)ethoxy]benzyl]-2-methoxy-5-sulfamoylbenzamide, and 4-amino- 5-chloro-2-methoxy-N-[4-[2-(1-pyrrolidinyl) ethoxy]benzyl] benzamide.

A compound of the present invention represented by general formula (I) can be administrated per os, e.g., in the form of pills or tablets, in which it may be present together with any of the usual pharmaceutical carriers, conventionally by compounding a compound of this invention together with a customary carrier or adjuvant, such as talc, magnesium stearate, starch, lactose, gelatin, any of numerous gums, or the like. Thus, in their most advantageous form, the compositions of this invention will contain a non-toxic pharmaceutical carrier in addition to the active ingredient of the present invention. Exemplary solid carriers are lactose, magnesium stearate, calcium stearate, starch, D-mannitol, crystalline cellulose, or the like. Representative liquid carriers are water, sesame oil, olive oil, propylane glycol, or the like. The active agents of this invention can be conveniently administered in such compositions containing active ingredient so as to be within the dosage range illustrated hereinafter. Thus, a wide variety of pharmaceutical forms suitable for many modes of administration and dosages may be employed. For oral administration, the active ingredient and pharmaceutical carrier may, for example, take the form of a powder, granule, pill, tablet, capsule, lozenge, elixir, syrup, or other liquid suspension or emulsion whereas, for parenteral administration, the composition may be in the form of a sterile solution. For intra-rectal administration, the composition may

be in the form of a suppository.

The method of using the compounds of this invention comprises internally or externally administering a compound of this invention, preferably orally or parenterally and preferably admixed with the pharmaceutical carrier, for example, in the form of any of the above compositions, or filled into a capsule, to alleviate conditions to be treated and symptoms thereof in a living animal body. Illustratively, it may be used in an amount of about 1.0 to about 1000 mg per day for oral administration, and about 1.0 to about 500 mg per day for a parenteral administration. The unit dose is preferably given a suitable number of times daily, typically three times.

The unit dose may vary depending upon the number of times given in any time period. Naturally, a suitable clinical dose must be adjusted in accordance with the condition, age, and weight of the patient, and it goes without saying that the enhanced activities of the compounds of the invention, together with their reduced side effects, also make them suitable for wide variations, and this invention therefore should not be limited by the exact ranges stated. The exact dosage, both unit dosage and daily dosage, will of course have to be determined according to established medical principles.

The following experiments show with the excellent effect of the present compounds (Compound No.means Example Compound No.), while using metoclopramide hydrochloride (III HCl) and trimethobenzamide hydrochloride (II HCl) as reference compounds.

Experiment 1

Contractile effects of the test compounds in isolated guinea pig ileum

Male Hartley guinea-pigs weighing about 450g were sacrificed and the ileum was excised. Then intact strips 1.5-2.0 cm long were prepared. These preparations were suspended vertically in an organ bath filled with Krebs-Henseleit's solution at 37 °C which was gassed with 95% O_2 and 5% CO_2. Rhythmic contractions of the preparations were isotonically measured. Effects of the test compounds were assessed as the relative percentage of a test compound against 10^{-6}M acetylcholine-induced contractions. Results were as follows (Table 1).

Table 1

Test compounds	ED_{50}(M)*
Compound 2	6.0×10^{-7}
Compound 3	4.6×10^{-7}
Compound 5	1.8×10^{-7}
Compound 6	4.0×10^{-7}
Compound 7	3.0×10^{-7}
Compound 8	1.6×10^{-6}
Compound 14	6.9×10^{-7}
Compound 19	4.2×10^{-7}
Compound 20	5.0×10^{-7}
Compound 23	3.0×10^{-7}
Compound 24	6.1×10^{-7}
Compound 25	6.8×10^{-7}
Compound 31	4.2×10^{-7}
Compound 32	1.4×10^{-7}
Compound 34	1.2×10^{-7}
Compound 35	4.9×10^{-7}
Compound 36	3.4×10^{-7}
Compound 37	1.8×10^{-7}

Compound 38	3.5×10^{-7}
Compound 39	3.9×10^{-7}
Compound 40	6.0×10^{-7}
Compound 41	1.3×10^{-7}
Compound 42	$< 10^{-7}$
Compound 43	$< 10^{-7}$
Compound 45	4.6×10^{-6}
Compound 47	3.0×10^{-6}
Compound 48	5.1×10^{-7}
Compound 51	6.1×10^{-7}
Compound 52	4.5×10^{-7}
Compound 53	4.6×10^{-7}
Compound 55	1.3×10^{-6}
Compound 56	3.2×10^{-7}
Compound 57	9.3×10^{-7}
Compound 58	4.2×10^{-7}
Compound 59	6.2×10^{-7}
Compound 62	3.9×10^{-7}
Compound 63	5.0×10^{-7}
Metoclopramide HCl	6.3×10^{-6}
Trimethobenzamide HCl	1.5×10^{-6}

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* The dose which evoked 50% of the acetylcholine-induced contraction.

These results showed that compound 2 had about 10 times and about 2.5 times stronger contractile effect than metoclopramide•HCl and trimethobenzamide•HCl respectively.

Experiment 2

Improving effects of the test compound on dopamine-induced suppression of gastrointestinal transit in mice

Male mice of the ddY strain weighing about 22 g were fasted overnight and the test compounds (suspended in 0.5% carboxymethylcellulose) were administered orally. Thirty minutes later dopamine (2 mg/kg dissolved in saline) or saline only was administered intraperitoneally followed immediately by the oral administration of charcoal meal (5% charcoal powder suspended in 10% gum arabic). Twenty minutes later the animals were sacrificed and the digestive tracts were isolated from the stomach to the cecum. The gastrointestinal transit was determined by calculating the total intestinal length between the pylorus and the cecum and the length over which charcoal meal was carried from the pylorus. Statistical analysis was carried out by Student's t-test for unpaired observations. Results were as follows (Table 2).

Table 2

Experimental group	Dose (mg/kg, p.o.)	n	Gastrointestinal transit (% ± S.E.)	Improvement (%)
Control	--	10	53.3 ± 2.0**	
Dopamine alone	--	12	31.7 ± 3.2	

Compound 2 + Dopamine	30	11	43.9 ± 2.8**	56.5
Control	--	11	53.3 ± 2.0**	
Dopamine alone	--	12	31.7 ± 3.2	
Compound 3 + Dopamine	30	10	44.0 ± 4.7*	56.9
Control	--	10	50.1 ± 3.0**	
Dopamine alone	--	10	25.0 ± 3.4	
Compound 18 + Dopamine	30	10	43.0 ± 6.5*	71.7
Control	--	12	51.8 ± 1.7**	
Dopamine alone	--	13	35.9 ± 2.1	
Compound 31 + Dopamine	30	12	45.2 ± 3.0*	58.5
Control	--	10	54.5 ± 3.4**	
Dopamine alone	--	10	32.9 ± 3.1	
Compound 34 + Dopamine	30	11	46.6 ± 3.4*	63.4
Control	--	22	50.9 ± 2.1**	
Dopamine alone	--	22	32.1 ± 2.0	
Metoclopramide ·HCl + Dopamine	30	9	37.2 ± 3.2	27.1
Control	--	22	50.9 ± 2.1**	

Dopamine alone	--	22	32.1 ± 2.0	
Trimethobenzamide •HCl + Dopamine	30	13	38.2 ± 3.8	32.4

* and **: Significantly different from groups treated with dopamine at $P<0.05$ and $P<0.01$, respectively.

It is concluded that the compounds of this invention showed significant improvement of gastrointestinal transit which was inhibited by dopamine at a dose of 30 mg/kg, but that the antiemetic drugs both metoclopramide•HCl and trimethobenzamide•HCl did not so only to a much lesser extent.

Experiment 3

Suppressing effects of the test compounds on apomorphine-induced emesis in beagle dogs

Male beagle dogs weighing about 8kg were fasted overnight. The test compounds (suspended or dissolved in 0.5% CMC) were administered orally and the dogs fed fortyfive minutes later. Then, fifteen minutes later 100mg/kg apomorphine (dissolved in saline) was administered subcutaneously and emetic events were observed for sixty minutes.

As a consequence, and as expected the antiemetic drugs metoclopramide HCl and trimethobenzamide•HCl showed the significant antiemetic effect at doses of 1mg/kg and 30mg/kg, respectively. The compound 2 shows however slight antiemetic effect at a dose of 30mg/kg.

Experiment 4

Acute toxicological study in mice

Male ICR mice aged 5 weeks were used for each determination. The test compounds (2-4 different doses) were intravenously administered and LD_{50} values were calculated using the up and down method. Results were as follows (Table 3).

Table 3

Test compounds	LD_{50} (mg/kg)
Compound 2	190.6
Compound 3	62.6
Compound 5	94.0
Compound 6	39.2
Compound 8	85.1
Compound 19	70.8
Compound 23	74.1
Compound 25	87.1
Compound 31	104.7
Compound 32	112.2
Compound 34	44.7
Compound 35	61.7
Compound 47	68.5
Compound 48	83.2
Compound 51	85.9
Compound 53	77.6

The following prescriptive examples and examples are given by way illustration only and are not to be construed as limitations of this invention, many variations of which are possible without departing from the scope and apirit thereof.

Prescriptive Example 1: Capsule Formulation (hard capsule)	
Compound of Example 2	50mg
Lactose	a proper quantity
Corn Starch	20mg
Magnesium Stearate	1mg
	to 130mg

Prescriptive Example 2: Tablet Formulation	
Compound of Example 5	50mg
Lactose	a proper quantity
Corn Starch	20mg
Magnesium Stearate	2mg
Hydroxypropylmethyl cellulose	8mg
Polyethyleneglycol	1mg
Titanium Oxide	1mg
	to 210mg

Prescriptive Example 3: Granule Formulation	
Compound of Example 2	100mg
Lactose	a proper quantity
D-Mannitol	500mg
Hydroxypropyl cellulose	20mg
Talc	2mg
	to 1000mg
Prescriptive Example 4: Injection Formulation	
Compound of Example 6 (hydrochloride)	50mg
Citric acid	0.5mg
Sodium Hydroxide	a proper quantity
Distilled Water for Injection	a proper quantity
	to 1ml
Prescriptive Example 5: Suppository Formulation	
Compound of Example 48 (hydrochloride)	50mg
Hard Fat	1250mg
	to 1300mg

Reference 1

4-[2-(Dimethylamino)ethoxy] benzaldehyde

To a solution of 61.1g of p-hydroxybenzaldehyde in 240ml of N,N-dimethylformamide was added 138g of potassium carbonate, 80.7g of 2-dimethylaminoethyl chloride and 30ml of isopropyl ether. The mixture was stirred at 60 °C for 1.5 hours. After cooling, the reaction mixture was poured into 720ml of water, and the whole was extracted with chloroform. The chloroform layer was extracted with aqueous hydrochloric acid. The aqueous layer was made alkaline with aqueous sodium hydroxide solution and extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was distilled to give 69.1g of colorless oil, b.p. 142-144 °C (4mmHg).

NMR spectrum δ ($CDCl_3$)ppm: 2.34 (6H,s), 2.76 (2H,t,J=6Hz), 4.15 (2H,t,J=6Hz), 7.02 (2H,d,J=9Hz), 7.82 (2H,d,J=9Hz),9.87 (1H,s).

Reference 2

4-[2-(1-Pyrrolidinyl)ethoxy]benzaldehyde

A mixture of 2.29g of 4-(2-bromoethoxy)benzaldehyde, 1.42g of pyrrolidine and 2.07g of potassium carbonate in 8ml of N,N-dimethylformamide was stirred at 60 °C for 2 hours. After cooling, water was added and the whole was extracted with ethyl acetate. The ethyl acetate layer was extracted with aqueous hydrochloric acid. The aqueous layer was made alkaline with potassium carbonate and extracted with ethyl acetate. The extract was washed with water, dried and evaporated. The residue was distilled to give 1.72g of colorless oil, b.p. 170 °C(5mmHg).

NMR spectrum δ ($CDCl_3$)ppm: 1.60-2.27 (4H,m), 2.44-2.80 (4H,m), 2.93 (2H,t,J=6Hz), 4.19 (2H,t,J=6Hz), 7.01 (2H,d,J=9Hz), 7.82 (2H,d,J=9Hz), 9.87.(1H,s).

In the same manner as described in Reference 1 and 2, the compound in Reference 3 was prepared.

Reference 3

4-(2-Piperidinoethoxy)benzaldehyde Colorless oil, b.p. 160-162 °C (6mmHg).

NMR spectrum δ ($CDCl_3$)ppm: 1.12-1.76 (6H,m), 2.27-2.61 (4H,m), 2.79 (2H,t,J=6Hz), 4.18 (2H,t,J=6Hz), 7.00 (2H,d,J=9Hz), 7.82 (2H,d,J=9Hz), 9.87 (1H,s).

Reference 4

4-[2-(Dimethylamino)ethoxy]benzaldoxime

A mixture of 154g of 4-[2-(dimethylamino)ethoxy]benzaldehyde and 59.9g of hydroxylamine hydrochloride in 600ml of ethanol was boiled for 10 minutes. After cooling, the precipitate was filtered to give hydrochloride as pale yellow crystals, m.p.174-175 °C. These crystals were dissolved in 150ml of water. The solution was made alkaline with potassium carbonate and extracted with chloroform. The extract was dried and evaporated. The residue was washed with isopropyl ether to give 157g of colorless crystals, which were recrystallized from ethyl acetate as colorless flakes, m.p. 95-96 °C.

Analysis for $C_{11}H_{16}N_2O_2$:
Calculated %: C, 63.44; H, 7.74; N, 13.45.
Found %: C, 63.28; H, 7.71; N, 13.37.

In the same manner as described in Reference 4, the compounds in References 5 and 6 were prepared.

Reference 5

4-[2-(1-Pyrrolidinyl)ethoxy]benzaldoxime hydrochloride:
Colorless plates, m.p. 219-220.5 °C (EtOH).

Analysis for $C_{13}H_{18}N_2O_2 \cdot HCl$:
Calculated %: C,57.67; H,7.07; N,10.35.
Found %: C,57.57; H,7.15;: N,10.25.

Reference 6

4-(2-Piperidinoethoxy)benzaldoxime hydrochloride
Colorless flakes, m.p. 224-225 °C (EtOH).

Analysis for $C_{14}H_{20}N_2O_2 \cdot HCl$:
Calculated %: C, 59.05; H, 7.43; N, 9.84.
Found %: C, 58.74; H, 7.28; N, 9.64.

Reference 7

4-(2-Piperidinoethoxy)benzylamine

A suspension of 32.3g of 4-(2-piperidinoethoxy)benzaldoxime in 400ml of 10% methanolic ammonia was hydrogenated over 3.6g of Raney nickel catalyst at a pressure of 50kg/cm^2 and at 30 °C. The catalyst was filtered off and the filtrate was evaporated. The residue was distilled to give 27.7g of colorless oil, b.p. 185 - 190 °C (6 mm Hg).

NMR spectrum $\delta(CDCl_3)$ppm: 1.30-1.90 (8H, m), 2.40-2.60 (4H,m), 2.76 (2H,t,J = 6Hz), 3.79 (2H,s), 4.09 (2H,t,J = 6Hz), 6.86 (2H,d,J = 9Hz), 7.21 (2H,d,J = 9Hz).

In the same manner as described in Reference 7, the compounds in References 8 and 9 were prepared.

Reference 8

4-[2-(l-Pyrrolidinyl)ethoxy]benzylamine Colorless oil, b.p. 163-165 °C (3 mm Hg).

NMR spectrum δ $(CDCl_3)$ppm: 1.53 (2H,br), 1.70-1.90 (4H,m) 2.50-2.75 (4H,m), 2.89 (2H,t,J = 6Hz), 3.79 (2H,s), 4.10 (2H,t,J = 6Hz), 6.88 (2H,d,J = 9Hz), 7.22 (2H,d,J = 9Hz).

Reference 9

4-[2-(Dimethylamino)ethoxy]benzylamine Colorless oil, b.p. 142-144 °C (6 mm Hg).

NMR spectrum $\delta(CDCl_3)$ ppm: 1.45 (2H,s), 2.32 (6H,s), 2.71 (2H,t,J = 6Hz), 3.79 (2H,s), 4.05 (2H,t,J = 6Hz), 6.88 (2H,d,J = 9Hz), 7.21 (2H,d,J = 9Hz).

Example 1

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide

To a cooled solution of 20.0g of 4-[2-(dimethylamino)ethoxy]benzylamine in 60ml of toluene was added a solution of 21.7g of 3,4-dimethoxybenzoyl chloride (which was prepared with 19.7g of 3,4-dimethoxybenzoic acid and 38.5g of thionyl chloride in the usual manner) in 60ml of toluene with stirring. The mixture was stirred at room temperature for 30 minutes. To the mixture was added 120ml of water and 1 ml of concentrated hydrochloric acid. The aqueous layer was separated, washed with 20ml of toluene and made alkaline with 20% sodium hydroxide solution to give a precipitate, which was washed with isopropyl ether, of 37.0g of pale brownish crystals. Recrystallization of the crystals from ethanol and isopropyl ether gave the title compound as colorless needles, m.p. 111-112 °C.

Analysis for $C_{20}H_{26}N_2O_4$:
Calculated %: C, 67.02; H, 7.31; N, 7.82.
Found %: C, 66.96; H, 7.28; N, 7.78.

Example 2

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide hydrochloride

A solution of 3.23g of N-[4-[2-(dimethylamino)ethoxy]benzyl]-3,4-dimethoxybenzamide in ethanol was acidified by the addition of ethanolic hydrogen chloride. The precipitate was filtered and washed with a mixture of ethanol and isopropyl ether to give 3.22g of pale brownish crystals, which were recrystallized from ethanol as colorless prisms, m.p. 194-195 °C.

Analysis for $C_{20}H_{26}N_2O_4 \cdot HCl$:
Calculated %: C, 60.83; H, 6.89; N, 7.09.
Found %: C, 60.78; H, 6.99; N, 7.05.

Example 3

3,4-Methylenedioxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl]benzamide:

To a cooled solution of 20.0g of 4-[2-(1-pyrrolidinyl)ethoxy]benzylamine in 30ml of chloroform was added 17.7g of 3,4-methylenedioxybenzoyl chloride (which was prepared with 15.9g of piperonylic acid and 65.3g of thionyl chloride in the usual manner). The mixture was stirred at room temperature for 20 minutes and the solvent was evaporated. 150ml Of water was added to the residue and the mixture was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was washed with isopropyl ether to give 30.0g of colorless crystals, which were recrystallized from ethyl acetate as colorless needles, m.p. 93.5 - 94.5 °C.

Analysis for $C_{21}H_{24}N_2O_4$:
Calculated %: C, 68.46; H, 6.57; N, 7.60.
Found %: C, 68.44; H, 6.65; N, 7.45.

Example 4

2,4-Dimethoxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl]benzamide

To a cooled suspension of 1.82g of 2,4-dimethoxybenzoic acid in 10ml of tetrahydrofuran was added 1.09g of ethyl chloroformate and 1.01g of triethylamine. After stirring for 15 minutes, to the mixture was added a solution of 2.00g of 4-[2-(1-pyrrolidinyl)- ethoxy]benzylamine in 5ml of tetrahydrofuran. The mixture was stirred for 15 minutes and the solvent was evaporated. To the residue was added 10% hydrochloric acid, and the solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated to give 3.31g of the title compound as a colorless oil.

Mass spectrum m/z: 384 (M^+)
IR spectrum ν (liquid) cm^{-1}: 1648 (c=o)
NMR spectrum δ ($CDCl_3$) ppm; 1.62-1.97 (4H,m),
2.44-2.76 (4H,m), 2.88 (2H,t,J=6Hz), 3.84 (3H,s),
3.86 (3H,s), 4.09 (2H,t,J=6Hz), 4.58 (2H,d,J=5.5Hz),
6.46 (1H,d,J=2Hz), 6.59 (1H,dd,J=9,2Hz), 6.88 (2H,d,J=9Hz),
7.27 (2H,d,J=9Hz), 7.99 (1H,br), 8.21 (1H,d,J=9HZ).

Example 5

4-Amino-5-chloro-N-[4-[2-(dimethylamino)ethoxy]benzyl]-2-methoxybenzamide

To a cooled suspension of 2.49g of 4-amino-5-chloro-2-methoxy-benzoic acid in 15ml of chloroform were successivly added dropwise 1.26g of triethylamine and 1.35g of ethyl chloroformate with stirring. The mixture was stirred at the same temperature for 30 minutes. Next, to the mixture was added a solution of 2.00g of 4-[2-(dimethylamino)ethoxy]benzylamine in 10ml of chloroform with stirring. The mixture was stirred at room temperature for 14 hours and the solvent was evaporated. 10% Hydrochloric acid was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with chloroform. The extract was washed with water, dried, and evaporated. The residue was washed with ether to give 3.87g of slightly brownish crystals, which were recrystallized from ethanol to give colorless needles, m.p. 147-148 °C.

Analysis for $C_{19}H_{24}ClN_3O_3$:
Calculated %: C, 60.39; H, 6.40; N, 11.12.
Found %: C, 60.28; H, 6.46; N, 11.12.

Further, the free base was converted into the hydrochloride in the usual way using ethanolic hydrogen chloride as in Example 2. Recrystallization of the hydrochloride from ethanol gave colorless needles, m.p.

206.5-208 °C.

Analysis for $C_{19}H_{24}ClN_3O_3 \cdot HCl$:
Calculated %: C, 55.08; H, 6.08; N, 10.14.
Found %: C, 54.86; H, 6.21; N; 9.98.

Example 6

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-2-methoxy-5-sulfamoylbenzamide

To a cooled suspension of 14.3g of 2-methoxy-5-sulfamoylbenzoic acid in 60ml of tetrahydrofuran were successively added dropwise 6.25g of triethylamine and 7.45g of pivaloyl chloride with stirring. The mixture was stirred at the same temperature for 1 hour and then a solution of 10.0g of 4-[2-(dimethylamino)ethoxy]-benzylamine in 40ml of tetrahydrofuran was added dropwise with stirring. The mixture was stirred at room temperature for 14 hours and the solvent was evaporated. Hydrochloric acid (10%) was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate to give a precipitate, which was washed with water and ethyl acetate, of 16.6g of colorless crystals. Recrystallization of the crystals from ethanol gave the title compound as colorless needles, m.p. 154-155 °C.

Analysis for $C_{19}H_{25}N_3O_5S$:
Calculated %: C, 56.00; H, 6.18; N, 10.31.
Found %: C, 55.71; H, 6.21; N, 10.02.

Further, the free base was converted into the hydrochloride in the usual way. Recrystallization of the hydrochloride from methanol gave colorless needles, m.p. 122.5-123 °C.

Analysis for $C_{19}H_{25}N_3O_5S\ HCl \cdot 2H_2O$:
Calculated %: C, 47.55; H, 6.30; N, 8.75.
Found %: C, 47.47; H, 5.90; N, 8.72.

Example 7

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-5-dimethylaminosulfonyl 2-methoxybenzamide

To a cooled suspension of 3.20g of 5-dimethylaminosulfonyl-2-methoxybenzoic acid in 10ml of tetrahydrofuran were successively added dropwise 1.25g of triethylamine and 1.34g of ethyl chloroformate with stirring. The mixture was stirred at the same temperature for 30 minutes and then a solution of 2.00g of 4-[2-(dimethylamino)ethoxy]benzylamine in 10ml of tetrahydrofuran was added dropwise with stirring. The mixture was stirred at room temperature for 2 hours and the solvent was evaporated. Hydrochloric acid (10%) was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was dried and evaporated. The residue was washed with isopropyl ether to give 4.10g of colorless crystals, which were recrystallized from a mixture of ethyl acetate and ether to give colorless needles, m.p. 99.5-100.5 °C.

Analysis for $C_{21}H_{29}N_3O_5S$:
Calculated %: C, 57.91; H, 6.71; N, 9.65.
Found %: C, 57.69; H, 6.82; N, 9.38.

Example 8

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-4-sulfamoylbenzamide

To a cooled solution of 1.50g of 4-[2-(dimethylamino)ethoxy]-benzylamine and 0.87g of triethylamine in 10ml of chloroform was added 1.87g of 4-sulfamoylbenzyl chloride, which was prepared from 1.71g of 4-sulfamoylbenzoic acid with 16.3g of thionyl chloride in the usual way, with stirring. The mixture was stirred

at room temperature for 30 minutes and the solvent was evaporated. Hydrochloric acid (10%) was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was washed with ethyl acetate to give 1.19g of pale yellow crystals, which were recrystallized from ethanol to give colorless crystals, m.p. 173.5-174.5 °C.

Analysis for $C_{18}H_{23}N_3O_4S$:
Calculated %: C, 57.28; H, 6.14; N, 11.13.
Found %: C, 57.58; H, 6.40; N, 10.95.

Example 9

N-[4-[2-(Dimethylamino)ethoxy]benzyl]-4-fluorobenzamide

To a cooled solution of 2.00g of 4-[2-(dimethylamino)ethoxy]-benzylamine and 1.14g of triethylamine in 10ml of chloroform was added 1.80g of 4-fluorobenzoyl chloride, which was prepared from 1.59g of 4-fluorobenzoic acid with 7.77g of thionyl chloride. The mixture was stirred for 30 minutes and the solvent was evaporated. Hydrochloric acid (10%) was added to the residue and the aqueous solution was washed with ethyl acetate. The aqueous layer was made alkaline with potassium carbonate and was extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. The residue was washed with n-hexane to give 3.07g of pale yellow crystals, which were recrystallized from a mixture of ethanol and ether to give colorless needles, m.p. 113-114.5 °C.

Analysis for $C_{18}H_{21}FN_2O_2$:
Calcultated %: C, 68.34; H, 6.69; N, 8.85.
Found %: C, 68.31; H, 6.67; N, 8.73.

Further, the free base was converted into the hydrochloride in the usual way. Recrystallization of the hydrochloride from ethanol gave colorless plates, m.p. 165-166 °C.

Analysis for $C_{18}H_{21}FN_2O_2 \cdot HCl$:
Calculated %: C, 61.27; H, 6.28; N, 7.94.
Found %: C, 61.18; H, 6.29; N, 7.75.

Examples 10

2-Amino-N-[4-[2-(dimethylamino)ethoxy]benzyl]benzamide

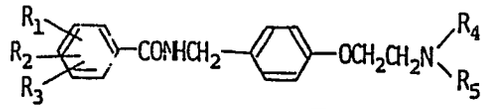
To a solution of 2.00g of 4-[2-(dimethylamino)ethoxy]benzylamine in 20ml of ethyl acetate was added 1.04g of isatoic anhydride. The mixture was stirred at room temperature for 15 minutes. Hydrochloric acid (10%) was added to the mixture. The aqueous layer was separated, made alkaline with potassium carbonate and extracted with ethyl acetate. The extract was washed with water, dried, and evaporated. Recrystallization of the residue from ethyl acetate gave 1.85g of colorless pillars, m.p. 104-105 °C.

Analysis for $C_{18}H_{23}N_3O_2$:
Calculated %: C, 68.98; H, 7.40; N, 13.41.
Found %: C, 69.07; H, 7.03; N, 13.32.

In the same manner as described in Examples 1 to 10, the compounds of Examples 11 to 86 were prepared.

The physical and chemical properties of the compounds of Examples 11 to 86 are shown in Tables 4 and 5.

Table 4



Example No.	R_1	R_2	R_3	R_4	R_5	salt	crystals	melting point (solvent)	Analysis for	(Calcd. C;H;N;, Found C;H;N;)	
11	2-OMe	3-OMe	H	Me	Me	fumarate	colorless needles	122~123° (EtOH)	$C_{20}H_{26}N_2O_4 \cdot C_4H_4O_4$	60.75; 6.37; 5.90	60.62; 6.41; 5.79
12	2-OMe	4-OMe	H	Me	Me	———	colorless needles	75~76° (EtOH-iPr_2O)	$C_{20}H_{26}N_2O_4$	67.02; 7.31; 7.82	67.04; 7.26; 7.57
13	2-OMe	6-OMe	H	Me	Me	———	colorless plates	130~131° (AcOEt)	$C_{20}H_{26}N_2O_4$	67.02; 7.31; 7.82	66.85; 7.29; 7.58
14	3-OMe	5-OMe	H	Me	Me	———	colorless needles	71~72° (EtOH-iPr_2O)	$C_{20}H_{26}N_2O_4$	67.02; 7.31; 7.82	66.90; 7.12; 7.59
15	3,4- -O> -O		H	Me	Me	———	colorless crystals	89~90° (EtOH-iPr_2O)	$C_{19}H_{22}N_2O_4$	66.65; 6.48; 8.18	66.61; 6.45; 8.03
	〃		〃	〃	〃	hydrochloride	colorless needles	166~167° (EtOH)	$C_{19}H_{22}N_2O_4 \cdot HCl$	60.24; 6.12; 7.39	60.13; 6.21; 7.16
16	3-OMe	4-OH	H	Me	Me	———	colorless plates	129.5~130.5° (AcOEt)	$C_{19}H_{24}N_2O_4$	66.26; 7.02; 8.13	66.34; 7.05; 7.97
17	3,4- -O> -O		H	$-(CH_2)_5-$		———	yellow needles	64~65° (AcOEt-iPr_2O)	$C_{22}H_{26}N_2O_4$	69.09; 6.85; 7.32	69.05; 6.74; 7.19
18	3-OMe	4-OMe	H	$-(CH_2)_4-$		———	colorless needles	93~95° (AcOEt-iPr_2O)	$C_{22}H_{28}N_2O_4$	68.73; 7.34; 7.29	68.61; 7.38; 7.09
19	3-OMe	4-OMe	H	$-(CH_2)_5-$		———	yellow needles	113~114° (AcOEt-iPr_2O)	$C_{23}H_{30}N_2O_4$	69.32; 7.59; 7.03	69.49; 7.73; 6.92
20	H	H	H	Me	Me	———	colorless plates	84~85° (iPr_2O)	$C_{18}H_{22}N_2O_2$	72.46; 7.43; 9.39	72.53; 7.25; 9.34
21	4-OH	H	H	Me	Me	———	colorless scales	133~134° (EtOH)	$C_{18}H_{22}N_2O_3$	68.77; 7.05; 8.91	69.04; 7.15; 8.95
22	2-OMe	H	H	Me	Me	———	colorless needles	72.5~73.5° (iPr_2O)	$C_{19}H_{24}N_2O_3$	69.49; 7.37; 8.53	69.40; 7.36; 8.33
	〃	〃	〃	〃	〃	hydrochloride	colorless needles	156.5~157.5° (EtOH)	$C_{19}H_{24}N_2O_3 \cdot HCl$	62.54; 6.91; 7.68	62.53; 6.99; 7.38
23	3-OMe	H	H	Me	Me	———	colorless needles	66~68° (iPr_2O)	$C_{19}H_{24}N_2O_3$	69.49; 7.37; 8.53	69.49; 7.13; 8.44
	〃	〃	〃	〃	〃	maleate	colorless plates	100~101° (iPrOH-iPr_2O)	$C_{19}H_{24}N_2O_3 \cdot C_4H_4O_4$	62.15; 6.35; 6.30	62.02; 6.26; 6.35
24	4-OMe	H	H	Me	Me	———	colorless needles	119~120° (EtOH-Et_2O)	$C_{19}H_{24}N_2O_3$	69.49; 7.37; 8.53	69.47; 7.29; 8.42
	〃	〃	〃	〃	〃	hydrochloride	colorless needles	175~176° (EtOH)	$C_{19}H_{24}N_2O_3 \cdot HCl$	62.54; 6.91; 7.68	62.46; 6.97; 7.52
25	4-OEt	H	H	Me	Me	———	colorless needles	128~129° (AcOEt)	$C_{20}H_{26}N_2O_3$	70.15; 7.65; 8.18	69.93; 7.75; 7.94
	〃	〃	〃	〃	〃	hydrochloride	colorless scales	164~165° (EtOH-Et_2O)	$C_{20}H_{26}N_2O_3 \cdot HCl$	63.40; 7.18; 7.39	63.15; 7.32; 7.23

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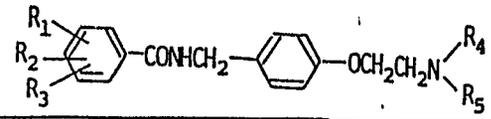
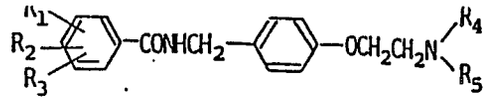


Example No.	R_1	R_2	R_3	R_4	R_5	salt	crystals	melting point (solvent)	Analysis for	(Calcd. C;H;N;, Found C;H;N;)	
26	4-OBu-n	H	H	Me	Me	———	colorless scales	131~132° (AcOEt)	$C_{22}H_{30}N_2O_3$	71.32; 8.16; 7.56	71.17; 8.26; 7.53
27	4-OMe	H	H	-$(CH_2)_4$-		———	colorless needles	120~121° (AcOEt)	$C_{21}H_{26}N_2O_3$	71.16; 7.39; 7.90	70.93; 7.54; 7.97
28	4-OEt	H	H	-$(CH_2)_4$-		———	colorless prisms	125~127° (AcOEt)	$C_{22}H_{28}N_2O_3$	71.71; 7.66; 7.60	71.57; 7.84; 7.52
29	3-OEt	H	H	Me	Me	———	colorless needles	80~81° (iPr_2O)	$C_{20}H_{26}N_2O_3$	70.15; 7.65; 8.18	70.03; 7.55; 8.09
30	4-OPr-n	H	H	Me	Me	———	colorless prisms	117~119° (AcOEt)	$C_{23}H_{30}N_2O_3$	70.76; 7.92; 7.86	70.58; 7.93; 7.81
31	3-OMe	4-OEt	H	Me	Me	———	colorless needles	113~114° (AcOEt)	$C_{23}H_{30}N_2O_4$	67.72; 7.58; 7.52	67.66; 7.61; 7.50
32	3-OEt	4-OEt	H	Me	Me	———	colorless needles	127.5~129° (AcOEt)	$C_{24}H_{32}N_2O_4$	68.37; 7.82; 7.25	68.39; 7.54; 7.11
33	3-OEt	5-OEt	H	Me	Me	———	colorless needles	114~114.5° (AcOEt)	$C_{24}H_{32}N_2O_4$	68.37; 7.82; 7.25	68.15; 7.73; 7.20
34	2-OMe	4-NH_2	5-Cl	-$(CH_2)_4$-		———	colorless needles	144~146.5° (EtOH)	$C_{21}H_{25}ClN_3O_3$	62.45; 6.49;10.40	62.49; 6.56;10.26
35	2-OMe	4-NH_2	5-Cl	-$(CH_2)_5$-		———	colorless needles	121~122° (AcOEt)	$C_{22}H_{28}ClN_3O_3$	63.23; 6.75;10.05	63.24; 6.80; 9.78
36	5-SO_2NHMe	2-OMe	H	Me	Me	———	colorless needles	154~156° (AcOEt-EtOH)	$C_{20}H_{27}N_3O_5S\cdot 1/2H_2O$	55.80; 6.56; 9.76	56.10; 6.61; 9.77
37	5-SO_2NH_2	2-OMe	H	-$(CH_2)_4$-		———	colorless crystals	91~93° (EtOH)	$C_{21}H_{27}N_3O_5S\cdot H_2O$	55.86; 6.47; 9.31	55.66; 6.35; 9.06
38	5-SO_2NH_2	2-OMe	H	-$(CH_2)_5$-		———	colorless needles	113~114° (EtOH)	$C_{22}H_{29}N_3O_5S\cdot H_2O$	56.76; 6.71; 9.03	56.81; 6.74; 8.84
	〃	〃	〃	〃		hydrochloride	colorless needles	203~204° (MeOH)	$C_{22}H_{29}N_3O_5S\cdot HCl$ $\cdot 1/4H_2O$	54.09; 6.29; 8.60	53.98; 6.28; 8.39
39	3-$SO_2N\cdot Me_2$	4-Cl	H	Me	Me	hydrochloride	colorless needles	146~147° (EtOH)	$C_{20}H_{28}ClN_3O_4S\cdot HCl$ $\cdot 1/2H_2O$	49.49; 5.81; 8.66	49.55; 5.83; 8.43
40	3-$SO_2N\cdot Me_2$	4-Cl	H	-$(CH_2)_4$-		fumarate	colorless prisms	110~111° (EtOH)	$C_{22}H_{28}ClN_3O_4S$ $\cdot C_4H_4O_4\cdot 1/2H_2O$	52.83; 5.63; 7.11	52.79; 5.64; 6.95
41	5-SO_2NH_2	2-OMe	4-NH_2	Me	Me	———	colorless needles	160~161° (EtOH)	$C_{19}H_{26}N_4O_5S$ $\cdot 1/2H_2O$	52.89; 6.31;12.98	52.89; 6.23;12.98
	〃	〃	〃	〃	〃	hydrochloride	colorless needles	134~136° (MeOH-AcOEt)	$C_{19}H_{26}N_4O_5S\cdot HCl$ $\cdot H_2O$	47.84; 6.13;11.75	48.12; 6.27;11.50
42	3-$SO_2N\ Me_2$	2-OMe	H	-$(CH_2)_4$-		———	colorless prisms	128~129° (EtOH)	$C_{23}H_{31}N_3O_5S$	59.85; 6.77; 9.10	59.89; 6.68; 9.10
43	5-SO_2NHMe	2-OMe	H	-$(CH_2)_4$-		———	colorless scales	168~169° (EtOH)	$C_{22}H_{29}N_3O_5S$	59.04; 6.53; 9.39	58.82; 6.24; 9.33



Example No.	R_1	R_2	R_3	R_4	R_5	salt	crystals	melting point (solvent)	Analysis for (Calcd. C;H;N;, Found C;H;N;)		
44	2-Cl	H	H	Me	Me	———	colorless needles	66~67° (iPr_2O)	$C_{18}H_{21}ClN_2O_2 \cdot 1/4H_2O$	64.09; 6.42; 8.30	64.24; 6.39; 8.07
	〃	〃	〃	〃	〃	hydrochloride	colorless scales	207~209° (EtOH)	$C_{18}H_{21}ClN_2O_2 \cdot HCl$	58.54; 6.00; 7.59	58.30; 6.07; 7.30
45	3-Cl	H	H	Me	Me	———	colorless needles	78~79° (iPr_2O)	$C_{18}H_{21}ClN_2O_2$	64.96; 6.36; 7.59	65.02; 6.37; 8.18
	〃	〃	〃	〃	〃	hydrochloride	colorless scales	166~167° ($EtOH-Et_2O$)	$C_{18}H_{21}ClN_2O_2 \cdot HCl$	58.54; 6.00; 7.59	58.27; 6.20; 7.26
46	4-Cl	H	H	Me	Me	———	colorless scales	105~106° ($EtOH-iPr_2O$)	$C_{18}H_{21}ClN_2O_2$	64.96; 6.36; 8.42	65.05; 6.42; 8.24
	〃	〃	〃	〃	〃	hydrochloride	colorless scales	186~188° (EtOH)	$C_{18}H_{21}ClN_2O_2 \cdot HCl$	58.54; 6.00; 7.59	58.46; 6.21; 7.21
47	3-Me	H	H	Me	Me	hydrochloride	colorless needles	118~120° ($EtOH-Me_2CO$)	$C_{19}H_{24}N_2O_2 \cdot HCl$	65.41; 7.22; 8.03	65.25; 7.19; 7.83
48	4-Me	H	H	Me	Me	———	colorless prisms	109~110° (iPr_2O)	$C_{19}H_{24}N_2O_2$	73.05; 7.74; 8.97	73.16; 7.61; 8.78
	〃	〃	〃	〃	〃	hydrochloride	colorless plates	197~199° ($EtOH-Et_2O$)	$C_{19}H_{24}N_2O_2 \cdot HCl$	65.41; 7.22; 8.03	65.20; 7.32; 7.70
49	4-Et	H	H	Me	Me	———	colorless pillars	101~102° (iPr_2O)	$C_{20}H_{26}N_2O_2$	73.59; 8.03; 8.58	73.65; 7.98; 8.38
50	2-NO_2	H	H	Me	Me	hydrochloride	colorless needles	190~191° (EtOH)	$C_{18}H_{21}N_3O_4 \cdot HCl$	56.92; 5.84;11.06	56.91; 6.05;10.82
51	3-NO_2	H	H	Me	Me	———	pale yellow needles	88~89° ($AcOEt-Et_2O$)	$C_{18}H_{21}N_3O_4$	62.96; 6.16;12.24	62.90; 6.24;12.18
	〃	〃	〃	〃	〃	hydrochloride	colorless needles	204~205° (EtOH)	$C_{18}H_{21}N_3O_4 \cdot HCl$	56.92; 5.84;11.06	56.95; 6.04;10.79
52	4-NO_2	H	H	Me	Me	———	pale yellow needles	153~154° (AcOEt)	$C_{18}H_{21}N_3O_4$	62.96; 6.16;12.24	62.94; 6.13;12.18
53	4-CN	H	H	Me	Me	———	pale yellow needles	93~94° ($AcOEt-Et_2O$)	$C_{19}H_{21}N_3O_2$	70.57; 6.55;12.99	70.41; 6.42;12.71
	〃	〃	〃	〃	〃	hydrochloride	pale yellow needles	182~183° (EtOH)	$C_{19}H_{21}N_3O_2 \cdot HCl \cdot 1/4H_2O$	62.63; 6.22;11.53	62.94; 6.13;11.25
54	4-tBu	H	H	Me	Me	———	colorless needles	135~137° (AcOEt)	$C_{22}H_{30}N_2O_2$	74.54; 8.53; 7.90	74.60; 8.28; 7.86
55	4-N·Me_2	H	H	Me	Me	———	colorless needles	144~146° (AcOEt)	$C_{20}H_{27}N_3O_2$	70.35; 7.97;12.31	70.21; 7.58;12.02
56	4-Me	H	H	-(CH_2)$_4$-		———	colorless prisms	105~107° (AcOEt)	$C_{21}H_{26}N_2O_2$	74.53; 7.74; 8.28	74.63; 7.44; 8.19
57	4-CN	H	H	-(CH_2)$_4$-		———	colorless prisms	102~103° (AcOEt)	$C_{21}H_{23}N_3O_2$	72.18; 6.63;12.03	71.96; 6.49;11.80

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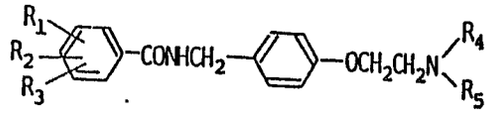

Example No.	R_1	R_2	R_3	R_4	R_5	salt	crystals	melting point (solvent)	Analysis for (Calcd. C;H;N;, Found C;H;N;)		
58	3-NO_2	H	H	-$(CH_2)_4$-		hydrochloride	grayish brown needles	176~178° (EtOH)	$C_{20}H_{23}N_3O_4 \cdot HCl$	59.18; 5.96;10.35	58.90; 5.97;10.39
59	2-Cl	4-Cl	H	Me	Me	———	colorless needles	111~112° (C_6H_6)	$C_{18}H_{20}Cl_2N_2O_2$	58.87; 5.49; 7.63	58.89; 5.46; 7.51
	〃	〃	〃	〃	〃	hydrochloride	colorless scales	218~219° (EtOH)	$C_{18}H_{20}Cl_2N_2O_2 \cdot HCl$	53.55; 5.24; 6.94	53.41; 5.39; 6.78
60	3-Cl	4-Cl	H	Me	Me	hydrochloride	colorless needles	209.5~212° (MeOH)	$C_{18}H_{20}Cl_2N_2O_2 \cdot HCl$	53.55; 5.24; 6.94	53.75; 5.47; 6.89
61	3-Cl	5-Cl	H	Me	Me	hydrochloride	colorless needles	159~160° (EtOH)	$C_{18}H_{20}Cl_2N_2O_2 \cdot HCl$	53.55; 5.24; 6.94	53.46; 5.46; 6.71
62	3-Me	4-NO_2	H	Me	Me	———	yellow needles	88~90° (AcOEt)	$C_{19}H_{23}N_3O_4$	63.85; 6.49;11.76	63.56; 6.61;11.70
	〃	〃	〃	〃	〃	hydrochloride	colorless prisms	170~171° (EtOH-Et_2O)	$C_{19}H_{23}N_3O_4 \cdot HCl$	57.94; 6.14;10.67	57.66; 6.38;10.63
63	3-Me	4-NO_2	H	-$(CH_2)_4$-		———	pale yellow prisms	113~114° (AcOEt)	$C_{21}H_{25}N_3O_4$	65.78; 6.57;10.96	65.49; 6.68;10.87
64	4-Me	H	H	-$(CH_2)_5$-		———	colorless needles	90~91° (iPr_2O)	$C_{22}H_{29}N_2O_3$	74.97; 8.01; 7.95	74.93; 7.81; 7.85
65	2-OEt	H	H	Me	Me	hydrochloride	colorless prisms	127~130° (EtOH-n-C_6H_{14})	$C_{20}H_{26}N_2O_3 \cdot HCl$	63.40; 7.18; 7.39	63.14; 7.32; 7.41
66	2-OH	H	H	Me	Me	hydrochloride	colorless needles	153~156° (EtOH)	$C_{18}H_{22}N_2O_3 \cdot HCl$	61.62; 6.61; 7.98	61.63; 6.66; 7.95
67	3-OH	H	H	Me	Me	———	colorless plates	151~153° (EtOH)	$C_{18}H_{22}N_2O_3$	68.77; 7.05; 8.91	68.94; 7.21; 8.98
68	3-SO_2NH_2	H	H	Me	Me	———	colorless crystals	169~172° (EtOH)	$C_{18}H_{23}N_3O_4S$	57.28; 6.14;11.13	57.30; 6.07;11.12
69	2-Me	H	H	Me	Me	hydrochloride	colorless scales	186~187.5° (EtOH)	$C_{19}H_{24}N_2O_2 \cdot HCl$	65.41; 7.22; 8.03	65.34; 7.14; 8.00
70	2-F	H	H	Me	Me	———	colorless needles	70~72° (AcOEt-n-C_6H_{14})	$C_{18}H_{21}FN_2O_2$	68.34; 6.69; 8.85	68.24; 6.57; 8.87
	〃	〃	〃	〃	〃	hydrochloride	colorless needles	139~142° (EtOH-Et_2O)	$C_{18}H_{21}FN_2O_2 \cdot HCl$	61.27; 6.28; 7.94	61.25; 6.30; 7.97
71	3-F	H	H	Me	Me	———	colorless needles	86~87° (iPr_2O)	$C_{18}H_{21}FN_2O_2$	68.34; 6.69; 8.85	68.34; 6.66; 8.83
	〃	〃	〃	〃	〃	fumarate	colorless plates	127~128° (EtOH)	$C_{18}H_{21}FN_2O_2 \cdot C_4H_4O_4$	61.10; 5.83; 6.48	60.94; 5.88; 6.55
72	3-NH_2	H	H	Me	Me	hydrochloride	colorless crystals	173~174° (MeOH-AcOEt)	$C_{18}H_{23}N_3O_2 \cdot 2HCl$	55.96; 6.52;10.88	56.13; 6.49;10.89

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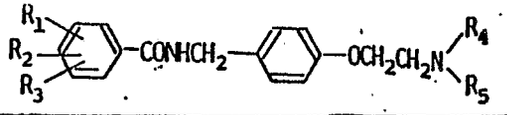


Example No.	R_1	R_2	R_3	R_4	R_5	salt	crystals	melting point (solvent)	Analysis for	(Calcd. C;H;N;, Found C;H;N;)	
73	4-NH_2	H	H	Me	Me	hydrochloride	colorless needles	171~173° (MeOH)	$C_{18}H_{23}N_3O_2 \cdot 2HCl$	55.96; 6.52;10.88	55.89; 6.69;10.88
74	3-CN	H	H	Me	Me	——	colorless crystals	99~100° (AcOEt-iPr_2O)	$C_{18}H_{21}N_3O_2$	70.57; 6.55;12.99	70.65; 6.51;12.99
	〃	〃	〃	〃	〃	hydrochloride	colorless prisms	155~157° (EtOH)	$C_{18}H_{21}N_3O_2 \cdot HCl$	63.42; 6.16;11.68	63.32; 6.14;11.73
75	3-tBu	4-OH	5-tBu	Me	Me	——	colorless plates	142~144° (Me_2CO-iPr_2O)	$C_{26}H_{38}N_3O_3$	73.20; 8.98; 6.57	73.47; 8.96; 6.29
76	3-Cl	4-NH_2	5-Cl	Me	Me	hydrochloride	pale brown needles	132~134° (EtOH)	$C_{18}H_{21}Cl_2N_3O_2 \cdot HCl \cdot 1/2H_2O$	50.54; 5.42; 9.82	50.55; 5.51; 9.71
77	3-Cl	4-NH_2	5-Cl	$-(CH_2)_4-$		——	pale brown needles	63~64° (AcOEt)	$C_{28}H_{33}Cl_2N_3O_2$	58.83; 5.68;10.29	59.00; 6.04;10.19
78	2-F	4-F	5-F	Me	Me	——	colorless prisms	80~82° (AcOEt)	$C_{18}H_{19}F_3N_2O_2$	61.36; 5.44; 7.95	61.32; 5.71; 7.98

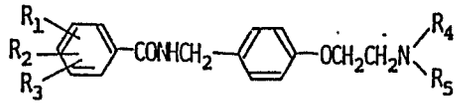
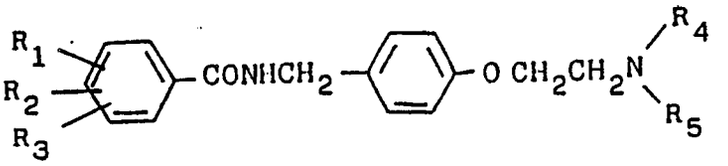


Table 5

Example No.	R_1	R_2	R_3	R_4	R_5		Ms spectrum m/z (M)	IR spectrum ν (liq)cm^{-1}	NMR spectrum δ ($CDCl_3$)ppm
79	3-OMe	H	H	-(CH_2)$_4$-		yellow oil	354	1650 (C=O)	1.66-1.98(4H,m), 2.44-2.76(4H,m), 2.88(2H,t,J=6HZ), 3.82(3H,s), 4.09(2H,t,J=6Hz), 4.61(2H,d,J=5.5Hz), 6.47(1H,br), 6.97(2H,d,J=9Hz), 7.20-7.38(6H,m)
80	3-SO_2NH_2	4-Cl	H	Me	Me	pale yellow oil	413,411 (1:3)	1648 (C=O)	2.29(6H,s), 2.69(2H,t,J=5.5Hz), 3.92(2H,br), 3.99(2H,t,J=5.5Hz), 4.47(2H,d,J=5.5Hz), 6.78(2H,d,J=9Hz), 7.07(1H,t,J=5.5Hz), 7.49(1H,d,J=8.5Hz), 7.92(1H,dd,J=8.5, 2Hz), 8.32(1H,d,J=2Hz)
81	3-SO_2NH·Me	4-Cl	H	Me	Me	colorless oil	427,425 (1:3)	1650 (C=O)	2.32(6H,s), 2.62(3H,s), 2.71(2H,t,J=5.5Hz), 4.04(2H,t, J=5.5Hz), 4.54(2H,d,J=5.5Hz), 5.88(1H,br), 6.85(2H,d, J=9Hz), 7.25(2H,d,J=9Hz), 7.56(1H,d,J=8.5Hz), 7.99(1H,dd, J=8.5,2Hz), 8.39(1H,d,J=2Hz)
82	3-SO_2NH_2	4-Cl	H	-(CH_2)$_4$-		yellow oil	439,437 (1:3)	1644 (C=O)	1.55-1.97(4H,m), 2.32-2.72(4H,m), 2.87(2H,t,J=6Hz), 4.07(2H,t,J=6Hz), 4.52(2H,br), 6.82(2H,d,J=9Hz), 7.09(2H,d,J=9Hz), 7.36(1H,d,J=8.5Hz), 7.70(1H,br), 7.83(1H,dd,J=8.5,2Hz), 8.34(1H,d,J=2Hz)
83	3-SO_2NH·Me	4-Cl	H	-(CH_2)$_4$-		yellow oil	453,451 (1:3)	1644 (C=O)	1.57-1.98(4H,m), 2.34-2.77(4H,m), 2.88(2H,t,J=5.5Hz), 4.08(2H,t,J=5.5Hz), 4.53(2H,d,J=5.5Hz), 6.84(2H,d,J=9Hz), 7.16(1H,br), 7.25(2H,d,J=9Hz), 7.55(1H,d,J=8.5Hz), 8.03(1H,dd,J=8.5,2Hz), 8.40(1H,d,J=2Hz)
84	3-SO_2N·Me_2	4-OMe	H	Me	Me	colorless oil	435	1644 (C=O)	2.32(6H,s), 2.71(2H,t,J=5.5Hz), 2.82(6H,s), 3.95(3H,s), 4.04(2H,t,J=5.5Hz), 4.53(2H,d,J=5.5Hz), 6.86(2H,d,J=9Hz), 7.03(1H,d,J=8.5Hz), 7.27(2H,d,J=9Hz), 8.10(1H,dd,J=8.5, 2.5Hz), 8.25(1H,d,J=2.5Hz)
85	3-SO_2N·Me_2	4-OMe	H	-(CH_2)$_4$-		pale yellow oil	461	1646 (C=O)	1.62-1.89(4H,m), 2.45-2.75(4H,m), 2.83(6H,s), 2.89(2H,t, J=6Hz), 3.96(3H,s), 4.10(2H,t,J=6Hz), 4.55(2H,d,J=5.5Hz), 6.88(2H,d,J=9Hz), 7.05(1H,d,J=8.5Hz), 7.27(2H,d,J=9Hz), 8.12(1H,dd,J=8.5,2Hz), 8.22(1H,d,J=2Hz)
86	2-F	4-F	5-F	-(CH_2)$_4$-		yellow oil	378	1660 (C=O)	1.57-2.10(4H,m), 2.48-2.80(4H,m), 2.90(2H,t,J=6Hz), 4.10(2H,t,J=6Hz),4.48-4.72(2H,m), 6.67-7.14(2H,m), 6.89(2H,d,J=9Hz), 7.25(2H,d,J=9Hz), 7.73-8.13(1H,m)

Claims

1) Amide-compound selected from those represented by the formula (I),



(I)

wherein R1 represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino which can be substituted by lower alkyl, nitro, cyano, sulfamoyl which can be substituted by lower alkyl, R2 represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino, nitro, and wherein R_1 and R_2 can be combined to form methylenedioxy R_3 means hydrogen, lower alkyl, halogen, or amino, and wherein R_4 and R_5 may be the same or different and each represents lower alkyl and wherein R_4 and R_5 may be combined together with nitrogen to form 1-pyrrolidinyl or piperidino, and pharmacologically-acceptable acid-addition salts thereof.

2) A compound of claim 1 which is N-[4-[2-(dimethylamino) ethoxy]-benzyl]-3,4-dimethoxybenzamide.

3) A compound of claim 1 which is N-[4-[2-(dimethylamino) ethoxy]-benzyl]-3,4-dimethoxybenzamide hydrochloride.

4) A compound of claim 1 which is 3,4-Methylenedioxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl] benzamide.

5) A compound of claim 1 which is 3,4-Dimethoxy-N-[4-[2-(1-pyrrolidinyl)ethoxy]benzyl]benzamide.

6) A compound of claim 1 which is N-[4-[2-(dimethylamino)ethoxy]benzyl]-4-ethoxy-3-methoxybenzamide.

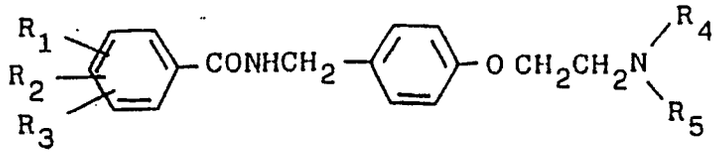
7) A compound of claim 1 which is N-[4-[2-(dimethylamino)ethoxy]benzyl]-2-methoxy-5-sulfamoylbenzamide.

8) A compound of claim 1 which is 4-Amino-5-chloro-2-methoxy-N-[4-[2-(l-pyrrolidinyl)ethoxy]benzyl]-benzamide.

9) A pharmaceutical composition useful to activate gastric motor function comprising one or more compounds as claimed in claims 1-8, in an amount effective for such purpose, together with a compatible, pharmaceutically-acceptable carrier or coating.

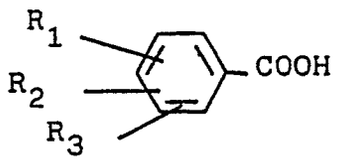
10) A method for the treatment of a subject suffering from an ailment associated with inadequate gastric motor function, comprising the step of administering to the said subject an amount of a compound of claims 1-8 which is effective for alleviation of such ailment.

11) A process for preparing amide-compounds represented by the formula (I) and pharmacologically-acceptable acid-addition salts thereof



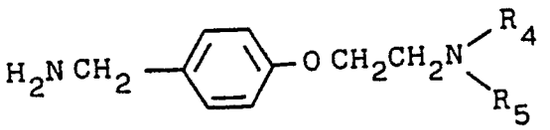
(I)

wherein R_1 represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino which can be substituted by lower alkyl, nitro, cyano, sulfamoyl which can be substituted by lower alkyl, R_2 represents hydrogen, lower alkoxy, hydroxy, lower alkyl, halogen, amino, nitro, and R_1 and R_2 can be combined to form methylenedioxy, R_3 means hydrogen, lower alkyl, halogen, or amino, R_4 and R_5 may be the same or different and each represents lower alkyl or R_4 and R_5 may be combined together with nitrogen to form 1-pyrrolidinyl or piperidino, which comprises reacting a functional derivative such as the chloride or other halide, the anhydride or a mixed anhydride, of a carbonic acid represented by the formula



(IV)

wherein R_1, R_2 and R_3 each has the same meaning as described above, with an amino-compound presented by the following formula,



wherein R_4 and R_5 each has the same meaning as described above, in the presence or in the absence of a base and in the presence of an organic solvent.

European Patent Office

PARTIAL EUROPEAN SEARCH REPORT

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

Application number

EP 88114257.4

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
A	DE - A - 1 493 828 (HOFFMANN-LA ROCHE) * Claims; page 16, lines 4-25 * --	1,9,11	C 07 C 103/82 C 07 C 121/52 C 07 C 143/78 C 07 D 295/08 C 07 D 317/68 C 07 C 102/00 A 61 K 31/165 A 61 K 31/18 A 61 K 31/33
A	DE - B - 1 069 640 (HOFFMANN-LA ROCHE) * Totality * ----	1,9,11	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

C 07 C 103/00
C 07 C 121/00
C 07 C 143/00
C 07 D 295/00
C 07 D 317/00

INCOMPLETE SEARCH

The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.

Claims searched completely:

Claims searched incompletely: 1,9-11

Claims not searched:

Reason for the limitation of the search: 10 Method for treatment of the human or animal body by therapy, art. 52(4) EPC

Place of search	Date of completion of the search	Examiner
VIENNA	18-11-1988	HOFBAUER

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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